excluded, with an excess of the respective pyridine component. The precipitate which formed when the mixture cooled was quickly sucked off and dried under vacuum (≤1 mmHg) at 60 °C. After several hours of drying, recrystallization from a small volume of ethanol yielded a colorless hygroscopic product. The reaction of 1 (Table I) with NaI in absolute ethanol yielded compound 1a.

General Procedure for the Preparation of the N-(β-Acetoxyethyl)pyridinium Salts 4–6. 1a, 2, or 3 (0.1 mol) was dissolved or suspended in acetonitrile. Acetyl chloride (0.15 mol), also dissolved in a small amount of acetonitrile, was dropped into this mixture, which was being refluxed. This mixture was stirred, and all moisture was excluded. After a maximum of 4 h of heating, the solvent and the excess of acetyl chloride were evaporated under reduced pressure. The residue was solid or oleaginous. It was ground with dry ether or acetone. After washing, it was crystallized from ethanol, 2-propanol, or acetone, if necessary, with the addition of ethyl ester.

Pharmacology. Longitudinal muscle strips of the guinea pig ileum were isolated according to Paton and Rang.[24] They were derived from animals of 350–600 g and suspended in an organ bath at 37 °C, containing 10 mL of Tyrode's solution of the following composition (mM): NaCl, 137; KCl, 3.7; $CaCl_2$, 1.8; $MgCl_2$, 1.05; NaH_2PO_4, 0.2; $NaHCO_3$, 11.9; glucose, 5.5; hexamethonium chloride, 0.01. The bath was gassed with 5% CO_2 in O_2, the pH was 7.4 ± 0.5. Isotonic contractions were recorded on a kymograph with a magnification of 1:8. The load of the lever was 150 mg.

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References and Notes

(1) E. Dirks, A. Scherer, M. Schmidt, and G. Zimmer, *Arzneim.-Forsch.*, **20**, 55 (1970).
(2) E. Dirks, A. Scherer, M. Schmidt, and G. Zimmer, *Arzneim.-Forsch.*, **20**, 197 (1970).
(3) I. Hagedorn, W.-H. Gündel, J. Hoose, and Chr. Jenter, *Arzneim.-Forsch.*, **26**, 1273 (1976).
(4) I. Hagedorn and W. Hohler, *Arzneim.-Forsch.*, **26**, 1515 (1976).
(5) H. Oldiges and K. Schoene, *Arch. Toxicol.*, **26**, 193 (1970).
(6) K. Schoene, J. Steinhanses, and H. Oldiges, *Biochem. Pharmacol.*, **25**, 1955 (1976).
(7) D. Kuhnen-Clausen, *Eur. J. Pharmacol.*, **9**, 85 (1970).
(8) D. Kuhnen-Clausen, *Toxicol. Appl. Pharmacol.*, **23**, 443 (1972).
(9) D. Kuhnen-Clausen, *FEBS Lett.*, **39**, 61 (1974).
(10) D. Kuhnen-Clausen, in "Proceedings of the International Meeting on Cholinesterases and Cholinergic Receptors", Split, Yugoslavia, April, 1975, Vol. 47, E. Reiner, Ed., Croatica Chemica Acta, Zagreb, Yugoslavia, 1975, p 465.
(11) B. Belleau, H. Tani, and F. Lie, *J. Am. Chem. Soc.*, **87**, 2283 (1965).
(12) R. M. Krupka, ref 10, p 299.
(13) E. J. Ariëns and A. M. Simonis, in "Molecular Pharmacology", E. J. Ariens, Ed., Vol. I, Section II.A., Academic Press, New York and London, 1964.
(14) J. F. Moran and D. J. Triggle, in "Cholinergic Ligand Interactions", D. J. Triggle, J. F. Moran, and E. A. Barnard, Eds., Academic Press, New York and London, 1971.
(15) R. Bill, Diplomarbeit, University of Freiburg, i.Br., 1975.
(16) M. J. Astle and F. J. Donat, *J. Org. Chem.*, **25**, 507 (1960).
(17) H. Kuhnen, ref 10, p 371.
(18) We are gratefull to Dr. H. Kuhnen, Institut für Aerobiologie, Schmallenberg-Grafschaft, who kindly supplied us with the enzymological data.
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(20) Lachesine was a kind gift of the Gerhardt-Penick Ltd., Thornton Laboratories, Croydon, U.K.
(21) E. J. Ariëns and A. M. Simonis, *Ann. N.Y. Acad. Sci.* **144**, 842 (1967).
(22) E. J. Ariëns and A. J. Beld, *Biochem. Pharmacol.*, **26**, 913 (1977).
(23) S. K. Gupta, J. F. Moran, and D. J. Triggle, *Mol. Pharmacol.*, **12**, 1019 (1976).
(24) W. D. M. Paton and H. P. Rang, *Proc. R. Soc. London, Ser. B* **163**, 1 (1964).

Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. 6. Syntheses of 3-(Sulfamoylmethyl)-1,2-benzisoxazole Derivatives and Their Anticonvulsant Activities

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Several 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives were synthesized from 3-(bromomethyl)-1,2-benzisoxazole by the reaction with sodium bisulfite followed by chlorination and amination. Some of them displayed marked anticonvulsant activity in mice. The introduction of a halogen atom to the 5 position of the benzisoxazole ring caused increased activity and neurotoxicity; the substitution of a sulfamoyl group caused decreased activity. The activity of monoalkylated compounds might be the result of biotransformation. Among these compounds, 3-(sulfamoylmethyl)-1,2-benzisoxazole (1a) was thought to be the most promising as an anticonvulsant from the ratio of NTD_{50} and ED_{50}.

During the course of routine testing, it was noted that 3-(sulfamoylmethyl)-1,2-benzisoxazole[1] (1a, Scheme I) exerted a potent anticonvulsant effect as measured by protection against maximal electroshock (MES) seizure.

The present paper deals with the syntheses of several 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives and the results of their biological evaluation.

It is well known that some arylsulfonamides show anticonvulsant activity which is supposed to be due to the inhibition of carbonic anhydrase. However, 1a showed only a weak effect on carbonic anhydrase in vitro.[2] Therefore, derivatives of 1a might be of interest as novel anticonvulsants.

Chemistry. In the early work,[1] 1a was prepared by the chlorosulfonation and the successive amination of 1,2-benzisoxazol-3-acetic acid (11). In these reactions, 5-sulfamoyl-3-(sulfamoylmethyl)-1,2-benzisoxazole was also obtained as a side product, and the yield of 1a was very poor (7%). Therefore, another method was chosen to prepare derivatives of 1a.

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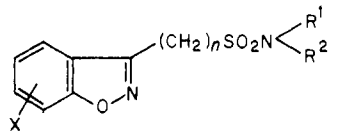
Table I



compd	X	n	$N<^{R^1}_{R^2}$	mp, °C	recrystn solvent	yield, %	formula[a]
1a	H	1	NH_2	160-163	AcOEt	65	$C_8H_8N_2O_3S$
b	H	1	$NHCH_3$	113-115	benzene	65	$C_9H_{10}N_2O_3S$
c	H	1	NHC_2H_5	76-78	benzene-hexane	66	$C_{10}H_{12}N_2O_3S$
d	H	1	NH-*i*-C_3H_7	114-117	benzene	46	$C_{11}H_{14}N_2O_3S$
e	H	1	$N(CH_3)_2$	105-107	MeOH	72	$C_{10}H_{12}N_2O_3S$
f	H	1	NH-*n*-C_3H_7	86-88	MeOH	31	$C_{11}H_{14}N_2O_3S$
g	H	1	NHOH	140-143	ether	97	$C_8H_8N_2O_4S$
h	H	1	$NHNH_2$	149-150 dec	AcOEt	47	$C_8H_9N_3O_3S$
i	H	1	$NHN(CH_3)_2$	113-114 dec	benzene	29	$C_{10}H_{13}N_3O_3S$
j	H	1	$NHCH_2CH_2OH$	138-141	AcOEt	24	$C_{10}H_{12}N_2O_4S$
k	H	1	$NHCH_2C_6H_5$	135-137	benzene	48	$C_{15}H_{14}N_2O_3S$
l	H	1	NHC_6H_5	139-141	benzene	46	$C_{14}H_{12}N_2O_3S$
m	H	1	NH-C_6H_4-2-$COOCH_3$	122-123	benzene-ether	10	$C_{16}H_{14}N_2O_5S$
n	H	1	$NH(CH_2)_3N(CH_3)_2$	113-115	benzene	22	$C_{13}H_{19}N_3O_3S$
o	H	1	c-NC_5H_{10}	134-137	benzene	85	$C_{13}H_{16}N_2O_3S$
p	H	1	c-$N(CH_2CH_2)_2O$	114-119	MeOH	70	$C_{12}H_{14}N_2O_4S$
q	H	1	c-$N(CH_2CH_2)_2N$-CH_3	119-121	benzene-hexane	27	$C_{13}H_{17}N_3O_3S$
r	H	1	c-$N(CH_2CH_2)_2N$-C_6H_5	140-142	MeOH	93	$C_{18}H_{19}N_3O_3S$
s	H	1	c-$N(CH_2CH_2)_2N$-$CH_2C_6H_5$	125-127	benzene-hexane	71	$C_{19}H_{21}N_3O_3S$
2a	5-F	1	NH_2	182-185	AcOEt	71	$C_8H_7FN_2O_3S$
b	5-F	1	$NHCH_3$	141-144	benzene	67	$C_9H_9FN_2O_3S$
c	5-F	1	NHC_2H_5	114-117	benzene	48	$C_{10}H_{11}FN_2O_3S$
d	5-F	1	NH-*i*-C_3H_7	127-130	benzene	42	$C_{11}H_{13}FN_2O_3S$
e	5-F	1	$N(CH_3)_2$	145-148	benzene	33	$C_{10}H_{11}FN_2O_3S$
f	5-F	1	c-$N(CH_2CH_2)_2NCH_3$	151-153	benzene	34	$C_{13}H_{16}FN_3O_3S$
3a	5-Cl	1	NH_2	192-195	AcOEt	26	$C_8H_7ClN_2O_3S$
b	5-Cl	1	$NHCH_3$	148-151	benzene	34	$C_9H_9ClN_2O_3S$
c	5-Cl	1	NHC_2H_5	150-152	benzene	37	$C_{10}H_{11}ClN_2O_3S$
d	5-Cl	1	NH-*i*-C_3H_7	114-116	benzene	20	$C_{11}H_{13}ClN_2O_3S$
e	5-Cl	1	$N(CH_3)_2$	176-179	benzene	37	$C_{10}H_{11}ClN_2O_3S$
4a	5-Br	1	NH_2	221-225	AcOEt	56	$C_8H_7BrN_2O_3S$
b	5-Br	1	$NHCH_3$	152-154	benzene	48	$C_9H_9BrN_2O_3S$
c	5-Br	1	NHC_2H_5	144-147	benzene	73	$C_{10}H_{11}BrN_2O_3S$
d	5-Br	1	NH-*i*-C_3H_7	95-97	benzene	52	$C_{11}H_{13}BrN_2O_3S$
e	5-Br	1	$N(CH_3)_2$	183-185	benzene	32	$C_{10}H_{11}BrN_2O_3S$
f	5-Br	1	c-$N(CH_2CH_2)_2NCH_3$	118-121	benzene-hexane	47	$C_{13}H_{16}BrN_3O_3S$
5	5-CH_3	1	NH_2	167-170	EtOH	70	$C_9H_{10}N_2O_3S$
6	5-NO_2	1	NH_2	226-229	EtOH	75	$C_8H_7N_3O_5S$
7	5-OCH_3	1	NH_2	178-181	AcOEt	25	$C_9H_{10}N_2O_4S$
8	6-F	1	NH_2	187-190	AcOEt	52	$C_8H_7FN_2O_3S$
9	7-CH_3	1	NH_2	147-150	AcOEt	48	$C_9H_{10}N_2O_3S$
16	H	2	NH_2	159-162	AcOEt	16	$C_9H_{10}N_2O_3S$
17	H	3	NH_2	136-138	AcOEt	49	$C_{10}H_{12}N_2O_3S$

[a] All compounds were analyzed for C, H, N, S, and halogen; analytical results were within ±0.4% of the theoretical values.

3-(Bromomethyl)-1,2-benzisoxazole[3] (**12**), which was prepared from **11** by bromination and successive decarboxylation, was reacted with sodium bisulfite and gave 1,2-benzisoxazole-3-methanesulfonic acid (**13**) (see Scheme I). The chlorination of **13** with phosphorus oxychloride afforded sulfonyl chloride **14**, which was converted to several derivatives of **1a** (**1**–**9**) by reactions with appropriate amines. 3-(Sulfamoylethyl)- (**16**) and 3-(sulfamoylpropyl)-1,2-benzisoxazole (**17**) (see Scheme I) were also prepared from 3-(chloroethyl)-[3] and 3-(chloropropyl)-1,2-benzisoxazole,[3] respectively.

The reduction of **6** with stannous chloride gave 5-amino-3-(sulfamoylmethyl)-1,2-benzisoxazole (**18**), which was easily acetylated with acetic anhydride to afford the 5-(acetylamino) derivative **19**. The reaction of **1a** with ethyl chloroformate and potassium carbonate gave *N*-(ethoxycarbonyl)-3-(sulfamoylmethyl)-1,2-benzisoxazole (**20**). Sulfonylurea derivative **21** was obtained from the ammonium salt of **20** by heating. The *N*-acetyl derivative of **1a** (**22**) was obtained by the acetylation of **1a** with acetyl chloride.

Biology and Discussion. Protection against MES was determined according to Swinyard,[4] and neurotoxicity was determined by the rotarod test[5] using mice.

Compounds **1f,h**–**p,r,s**, **5**–**7**, and **9** (see Table I) were ineffective at 100 mg/kg po. Median effective doses (ED_{50}) and median neurotoxic doses (NTD_{50}) were determined for the compounds which showed some activity at 100 mg/kg. ED_{50} values and NTD_{50} values summarized in Table II indicated marked activity against MES following administration of **1a**–**e,g,q**, **2a**–**f**, **3a**–**e**, **4a**–**f**, and **8** (see Table I).

The introduction of a halogen atom to the 5 or the 6 position of the benzisoxazole ring increased the potency. The order of increasing potency of those compounds was as follows: H < F < Cl < Br. The order of increasing neurotoxicity followed the order of increasing potency, and the increasing rate of neurotoxicity was larger than that of potency. As far as 5-halogeno derivatives were concerned, the order of increasing potency followed the order of increasing σ_m values[6] (H, 0.00; F, 0.34; Cl, 0.37; Br, 0.39). However, the introduction of a sulfamoyl (σ_m = 0.46) or

Scheme I

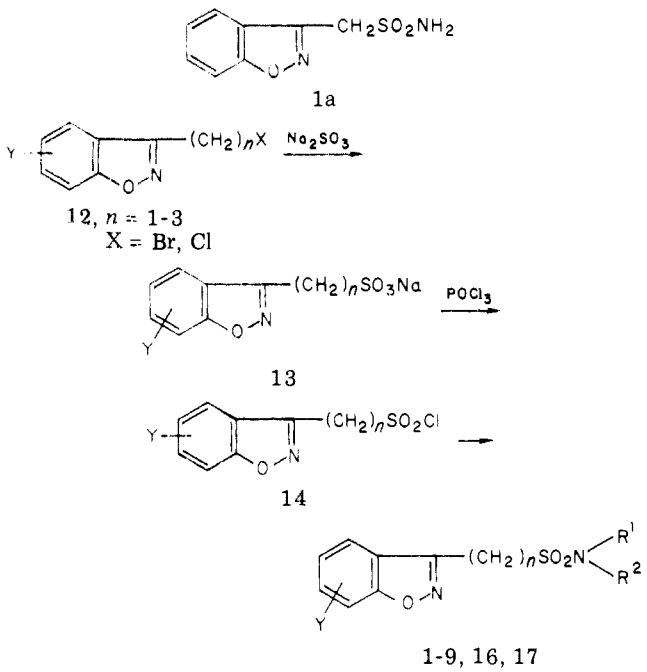


Table II. Anticonvulsant Activity and Neurotoxicity

compd	anti-MES; ED_{50}, mg/kg, po	neurotox; NTD_{50}, mg/kg, po
1a	20 (16-24)[a]	292 (252-330)
b	23 (14-37)	
c	39 (29-52)	223 (140-356)
d	56 (44-69)	340[b]
e	37 (28-49)	
g	32 (19-54)	
q	57 (46-66)	
2a	15 (10-20)	154 (134-175)
b	35 (25-45)	168 (141-202)
c	32 (23-41)	200[b]
d	38 (32-46)	109 (69-174)
e	32 (27-38)	350[b]
f	100[b]	142 (64-317)
3a	14 (10-21)	52 (38-70)
b	20 (16-25)	60 (44-83)
c	21 (17-27)	
d	100[b]	
e	57 (41-69)	250[b]
4a	14 (10-18)	60 (42-77)
b	15 (10-22)	
c	18 (14-23)	66 (55-79)
d	22 (16-32)	93 (59-146)
e	45 (33-58)	100-200
f	88 (72-108)	87 (60-127)
8	19 (8-46)	
16	26 (17-40)	
17	39 (23-67)	
diphenylhydantoin	10.0 (7.6-12.3)	111.0 (87.2-150)
metharbital	60.8 (79.2-97.6)	87.9 (79.2-97.6)

[a] 95% confidence limits. [b] Graphically calculated.

a nitro group (σ_m = 0.71) to the 5 position contributed to the loss of potency and no acceptable QSAR analysis could be obtained among these compounds.

The study of N-substituted compounds revealed that the introduction of simple monoalkyl substituents did not abolish activity, but when the substituent was an amino (**1h**), a dimethylamino (1i), a benzyl (**1k**) or larger the activity was generally lost. With the exception of dimethylamino (1e, 2e, 3e, and 4e) and *N*-(methylpiperazinyl) derivatives (**1q** and **4f**), the disubstituted compounds were inactive in the anticonvulsant test. The order of the decreasing potency for alkylated derivatives in each series of compounds 1–4 was as follows: $-SO_2NH_2$ > $-SO_2NHCH_3$ > $-SO_2NHEt$ = $-SO_2(CH_3)_2$ > $-SO_2$-*i*-Pr. This order is in general agreement with the relative extent of in vivo dealkylation of monoalkylated sulfonamide derivatives reported by Smith et al.[7] Therefore, the potency of these compounds might be the result of biotransformation.

Smith et al.[7] also reported that the parent sulfonamide was formed by in vivo reduction of *N*-hydroxybenzenesulfonamide. The potency of the *N*-hydroxy derivative of **1a** (**1g**) might be the result of in vivo reduction. Sulfamoylethyl derivative **16** and *N*-methyl derivative **1c** exhibited approximately equivalent ED_{50} values, and the ED_{50} value of sulfamoylpropyl derivative **17** was comparable to those of the *N*-ethyl derivative **1c** and *N*-dimethyl derivative **1e**.

Among these compounds, **1a** was thought to be the most promising compound as an anticonvulsant from the ratio of NTD_{50} and ED_{50}. The further investigation of **1a** is now in progress in our laboratories.

Experimental Section

Melting points were determined in a Yanagimoto apparatus and are uncorrected. The IR, NMR, and mass spectral data of all compounds were consistent with structure. Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

3-(Sulfamoylalkyl)-1,2-benzisoxazoles 1a, 2a, 3a, 4a, and 5-9 (Table I). General Procedure. To a solution of **12** (0.038 mol) in MeOH (130 mL) was added Na_2SO_3 (8.1 g, 0.064 mol) in H_2O (130 mL). The mixture was stirred at 50 °C for 4 h and evaporated in vacuo. To the residue was added MeOH (250 mL), and the insoluble material in MeOH was removed. The solution was concentrated, and the residue was washed with ether and dried. To the dried residue was added $POCl_3$ (100 mL), the mixture was refluxed for 3 h, and then the excess of $POCl_3$ was removed in vacuo. Thus, crude **14** was obtained. Crude **14** was dissolved in AcOEt (200 mL). Under cooling, NH_3 was saturated in the solution. The solid separated and was filtered off, and the solvent was removed. The residue was washed with AcOEt and recrystallized from the appropriate solvent.

***N*-Substituted 3-(Sulfamoylmethyl)-1,2-benzisoxazoles 1b–s, 2b–f, 3b–e, and 4b–f (Table I). General Procedure.** To the AcOEt solution of **14**, above mentioned, was added the appropriate amine (0.114 mol, 3 molar equiv), and the mixture was stirred at room temperature for 30 min. The solid separated and was filtered off, and the filtrate was evaporated in vacuo. The resulting residue was recrystallized from the appropriate solvent.

5-Amino-3-(sulfamoylmethyl)-1,2-benzisoxazole (18). To the suspension of **6** (11 g) in concentrated HCl was added a solution of $SnCl_2$ (60 g in 60 mL of concentrated HCl), and the mixture was stirred at 25–30 °C for 3 h. The solution was made alkaline with $NaHCO_3$ and extracted with AcOEt. After being dried over Na_2SO_4, the solvent was removed in vacuo. The recrystallization of the residue from MeOH gave 6 g of **18** (62%), mp 224–227 °C. Anal. ($C_8H_9N_3O_3S$) C, H, N, S.

5-(Acetylamino)-3-(sulfamoylmethyl)-1,2-benzisoxazole (19). To the solution of **18** (2.5 g) in pyridine (20 mL) was added Ac_2O (3.4 g). After being kept overnight at room temperature, the mixture was poured into H_2O and extracted with AcOEt. The extract was washed with H_2O and evaporated. The residue was recrystallized from MeOH to give 0.7 g of **19** (24%), mp 261–266 °C. Anal. ($C_{10}H_{11}N_3O_4S$) C, H, N, S.

***N*-(Ethoxycarbonyl)-3-(sulfamoylmethyl)-1,2-benzisoxazole (20).** To a solution of **1a** (4.0 g in 80 mL of acetone) were added ethyl chloroformate (6.1 g) and K_2CO_3 (7.8 g). The mixture was refluxed for 24 h and then filtered. The filtrate was evaporated, and the residual oil was dissolved in H_2O. The solution was acidified with HCl. The resulting precipitate was collected, washed with H_2O, and recrystallized from AcOEt to give **20** (4.0 g, 75%), mp 139–141 °C. Anal. ($C_{11}H_{12}N_2O_5S$) C, H, N, S.

***N*-Carbamino-3-(sulfamoylmethyl)-1,2-benzisoxazole (21).** A solution of **20** (2.0 g in 150 mL of MeOH) was saturated with

NH_3. After being kept at room temperature overnight, the solution was concentrated in vacuo to give the ammonium salt of **20** (2.0 g) which was heated on an oil bath (150–160 °C) under reduced pressure for 10 min. To the cooled residue was added AcOEt. The insoluble solid was collected and recrystallized from MeOH to give **21** (0.9 g, 53%), mp 189–194 °C. Anal. ($C_9H_9N_3O_4S$) C, H, N, S.

***N*-Acetyl-3-(sulfamoylmethyl)-1,2-benzisoxazole (22).** To 50 mL of AcCl was added **1a** (2.3 g). The mixture was refluxed for 48 h and then evaporated. The residue was washed with benzene, dried, and recrystallized from acetone to give **22** (2.5 g, 91%), mp 183–185 °C. Anal. ($C_{10}H_{10}N_2O_4S$) C, H, N, S.

Biological Methods. All experiments were carried out in male mice of STD-dd strain weighing 20–22 g. Diet and water were given ad libitum to animals until the time of experiment. All compounds were administered by gavage as a suspension of 5% tragacanth solution. In preliminary screenings, all compounds were tested for anticonvulsant activity at 100 mg/kg. For the determination of ED_{50} and NTD_{50}, groups of ten mice were used per dosage level, using at least four dosage levels.

Anticonvulsant Activity. Drugs were evaluated for their ability to prevent the hind-limb extensor component of maximal electroshock seizure induced using a 60-Hz, 25-mA current for 0.2 s, delivered through corneal electrodes 2 h after dosing. ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[8]

Neurotoxicity. NTD_{50} was determined employing the rotarod. The end point for minimal neurotoxicity was muscle incoordination and was based upon the inability of the mouse to retain on a horizontal rod (2.5-cm in diameter) rotating at 11 rpm 2 h after dosing. NTD_{50} values were calculated by the method of Litchfield and Wilcoxon.[8]

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References and Notes

(1) H. Uno and M. Kurokawa, unpublished results.
(2) Y. Masuda, T. Karasawa, Y. Shiraishi, M. Hori, K. Yoshida, and M. Shimizu, unpublished results.
(3) H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato (the late), and H. Nishimura, *Chem. Pharm. Bull.*, **24**, 632 (1972).
(4) E. A. Swinyard, *J. Am. Pharm. Assoc., Sci. Ed.*, **38**, 201 (1963).
(5) N. W. Dunham and T. S. Miya, *J. Am. Assoc., Sci. Ed.*, **46**, 208 (1957).
(6) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
(7) D. L. Smith, H. H. Keasling, and A. A. Forist, *J. Med. Chem.*, **8**, 520 (1965).
(8) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

Azetidine Derivatives of Tricyclic Antidepressant Agents

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Tricyclic derivatives of azetidine were synthesized and screened for their potential antidepressant activity. The active series had the tricyclic rings attached to position 1 and a basic group in position 3 of the azetidine. The most interesting compounds were comparable to the reference standards for reserpine antagonism in mice, the most active being the dextrorotatory methylamino derivative **84**.[1] The pharmacological profile classifies it as a CNS stimulant devoid of peripheral anticholinergic activity.

One of the best represented classes in the field of psychoactive drugs with antidepressant effects is without doubt that of the tricyclic antidepressant agents. There has been a great deal of research on these structures in attempts to separate the documented therapeutic activity from the side effects, which are for the most part associated with their anticholinergic and cardiotoxic activities.[1-5] The novelty of the products synthesized is based on the association of the azetidine ring with the tricyclic structure. Some derivatives of this series were found in pharmacological screening to have potential antidepressant activity, the most encouraging results coming from products with two aliphatic amine groups, which is uncommon in the field of drugs with antidepressant activity.

Chemistry. The *tert*-butyl derivatives in Table I were obtained by alkylation of suitable substrates with 3-chloro-1-*tert*-butylazetidine, prepared by the method of Gaertner.[6] The other compounds were prepared according to Scheme I.

The alkylation was found to be difficult for $n = 1$ and A = $-CH_2CH_2-$. Compound 11 was so obtained by reductive dealkylation of the corresponding unsaturated derivative (A = $-CH{=}CH-$), which alkylates more easily. The yields of alkylation were 40–60%. Reductive dealkylation was, as expected, difficult for A = S, so that only the *tert*-butyl derivatives **2–4** and the unsubstituted azetidine **1** were prepared. To carry out the reductive amination,[8] it was necessary to carefully control times and temperatures for the compounds with A = $-CH_2O-$, in order to avoid cleavage of the benzyl ether.

The azetidines of Table V were synthesized from the corresponding mesylates prepared by the method of Anderson[7]. Tables II–IV list the intermediates, with their physical properties and yields. The general scheme (Scheme II) of synthesis is shown below. The methods

Scheme I[a]

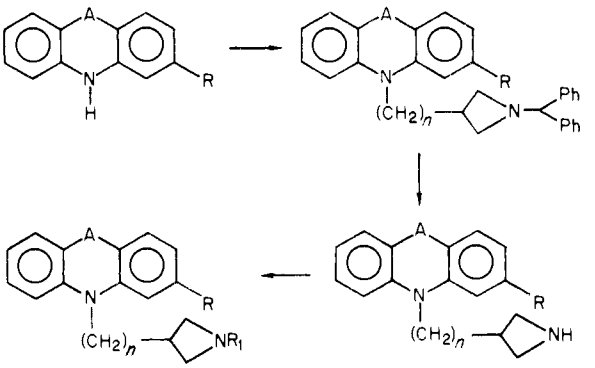

Table I

[a] For $n = 0$, the alkylating halide was a bromide;[7] for $n = 1$, a chloride.

